May 18, 2004

Via fax and UPS

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0118
ICH Q5E; Draft Guidance on Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process [Federal Register Volume 69, No. 61, page 16581, March 30, 2004]

Dear Sir/Madam:

Aventis Pharmaceuticals Inc. appreciates the opportunity to comment on the above-referenced draft guidance entitled *"Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process"*.

This draft guidance is intended to assist in the design and conduct of studies that establish the comparability of products following a change in the manufacturing process.

We offer the following comments/clarification for your consideration.

General Comments

The guideline remains too general. We agree that a case-by-case approach is needed for biotechnological/biological products. However, we recommend adding to the guideline some examples of changes for which the principles for assessing the comparability of biotechnological/biological products before and after changes may apply.

The use of Comparability Protocols (CP), as proposed by FDA in the September 2003 *Draft Guidance on Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing and Controls Information,* should also be included in this guideline, as this strategy has provided a useful tool in setting the appropriate testing and acceptance criteria for postapproval changes associated with biotechnological/biological products.

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Change in manufacturing sites are not specifically addressed in this guideline. It will be useful to include some basic requirements on the transfer of a product to another manufacturer or manufacturing site.

Specific Comments

Lines 9-11: *"The objective of this document is to provide principles for assessing the comparability of biotechnological/biological products before and after changes are made in the manufacturing process for the drug substance or drug product."*

And

Footnote 3: *For convenience, when the term "product" is used without modifiers, it is intended to refer to the intermediates, drug substance, and drug product.*

Recommendation: For more clarity, and consistency with the definition in Footnote 3, we propose the following wording: *"The objective...are made in the manufacturing process **of the product.**[1]"* In this case, we also suggest renaming Footnote 3 as Footnote 1.

Lines 11-15: *"This guideline is intended to assist in the design and conduct of studies used to collect the technical information to establish the comparability of pre-change and post-change products and, thereby, confirm that the manufacturing process changes did not have an adverse impact on the quality, safety and efficacy of the drug product."*

Recommendation: For clarity, we suggest revising the text to read as follows: *"This guideline is intended to assist in the design and conduct of studies used **to be performed** to collect the technical information **establishing** the comparability of pre-change and post-change products and, thereby, **to** confirm that the manufacturing process changes did not have an adverse impact on the quality, safety and efficacy of the drug product."*

Lines 21-23: *"When changes are made to the manufacturing process, the manufacturer generally evaluates the quality attributes of the product to demonstrate that modifications did not occur that would adversely impact the safety and efficacy of the drug product."*

Recommendation: All the quality attributes will not always need to be evaluated. Therefore, we recommend rewording this sentence to read as follows: *"When changes are made to the manufacturing process, the manufacturer generally evaluates the quality attributes of the product **that may be impacted by the change** to demonstrate that modifications did not occur that would adversely impact the safety and efficacy of the drug product."*

Lines 26-30: *"While ICH documents have not specifically addressed considerations for demonstrating comparability between pre-change and post-change products, several ICH documents have provided guidance for technical information and data to be submitted in marketing applications that can also be useful for assessing manufacturing process changes (see References)."*

Recommendation: For clarity, we suggest adding text to include the location of *"References"*. The sentence should read as follows: *"While ICH ...that can also be useful for assessing manufacturing process changes (see **Section 5.0** References)."*

Lines 34-36: *" • Assess the impact of observed differences in the quality attributes caused by the manufacturing process change for a given product as it relates to safety and efficacy."*

Recommendation: We suggest revising this bullet point to clarify that safety and efficacy apply to the drug product even for changes on the "product" (i.e., drug substance, intermediates, drug product). We suggest that the bullet point should read as follows: *" • Assess the impact of observed differences in the quality attributes caused by the manufacturing process change for a given product as it relates to safety and efficacy **of the drug product**."*

Footnote 1: *"For convenience, when the term "manufacturer" is used, it is intended to include any third party having a contractual arrangement to produce the intermediates, drug substance, or drug product on behalf of the marketing authorization holder (or the developer, if prior to market authorization)."*

Recommendation: For editorial consistency, we suggest revising "authorization" to read as **"authorisation".**

Lines 38-46: *" The principles adopted and explained in this document apply to:*

- *Proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures;*
- *Products where changes are made by a single manufacturer, including those made by a contract manufacturer, who can directly compare results from the analysis of pre-change and post-change products; and*
- *Products where process changes are made in development of for which a marketing authorisation has been granted."*

Recommendation: The wording of the scope remains too general. Only proteins, polypeptides and their derivatives are addressed in the guideline. It is not clear, if products from conventional fermentation, DNA products, oligonucleotides or heparins are included or not.

For clarity, we suggest revising the text of the last two bullet points to read as follows:

*" • Products where **manufacturing process** changes are made by a single manufacturer, including those made by a contract manufacturer, who can directly compare results from the analysis of pre-change and post-change products; and*
*• Products where **manufacturing** process changes are made in development of for which a marketing authorisation has been granted."*

Further, in order to make it clear that the ICH guideline covers only changes made in the manufacturing process by a single manufacturer, we recommend adding the following sentence: ***"The principles outlined in this document do not apply to comparison between manufacturing processes made from different manufacturers."***

Lines 49-52: *"The principles outlined in this document might also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids. Manufacturers are advised to consult with the appropriate regional regulatory Authorities to determine applicability."*

Recommendation: For clarity, we suggest that the Scope should include text to indicate whether or not this guidance applies to proteins and polypeptides isolated from tissues and body fluids. Therefore, an exclusion statement is needed.

Lines 54-57: *"The goal of the comparability exercise is to ensure the quality, safety and efficacy of the drug product produced by a changed manufacturing process through collection and evaluation of the relevant data to determine whether there is any adverse impact on the drug product due to the manufacturing process changes."*

Recommendation: The assessment of the impact of a manufacturing process change is not always obvious. Therefore recommend revising this sentence to read as follows: *"The goal of the comparability exercise is to ensure the quality, safety and efficacy of the drug product produced by a changed manufacturing process through collection and evaluation of the relevant data to determine whether there **may be** any adverse impact on the drug product due to the manufacturing process changes."*

Lines 70-71: *"To identify the impact of a manufacturing process change, a careful evaluation of all potential consequences n the product, not just the obvious, should be performed."*

Recommendation: The term *"obvious"* is unclear. We suggest that this word be removed or further clarified. Therefore, we recommend revising this sentence to read as follows: *"To identify the impact of a manufacturing process change, a careful evaluation of all **foreseeable** consequences on the product should be performed."*

Lines 84-87: *"• Although the products appear highly similar, there is doubt concerning the capability of the analytical procedures to discern relevant differences that can impact the safety and efficacy of the product. The manufacturer should consider performing additional nonclinical and/or clinical studies."*

Recommendation: To ensure this bullet point is consistent with the information that follows it, we recommend adding the following statement: *"• Although the products appear highly similar, there is doubt concerning the capability of the analytical procedures to discern relevant differences that can impact the safety and efficacy of the product. The manufacturer should consider performing additional nonclinical and/or clinical studies* ***to reach a definitive conclusion, taking into account characteristics of the drug product such as therapeutic window, clinical usage (acute vs. chronic administration), dosing characteristics, route of administration and potential for immunogenic responses.*** *"*

Lines 88-92: *"• Some differences have been observed in the quality attributes of the pre-change and post-change products, but it can be justified that no adverse consequence on safety or efficacy profiles is expected, based on the manufacturer's accumulated experience, relevant information, and data. In these circumstances, pre- and post-change products can be considered comparable."*

Recommendation: For consistent wording throughout the guidance, we suggest that the term *"consequence"* be replaced with the term *"impact"*. Therefore, we suggest revising this bullet point to read as follows: *"• Some differences have been observed in the quality attributes of the pre-change and post-change products, but it can be justified that no adverse* ***impact*** *on safety or efficacy profiles is expected, based on the manufacturer's accumulated experience, relevant information, and data. In these circumstances, pre- and post-change products can be considered comparable."*

Lines 93-101: *"• Although the pre- and post-change products are similar, some differences have been identified in the comparison of quality attributes and possible adverse consequences on safety and efficacy profiles cannot be excluded. The manufacturer should consider performing nonclinical and/or clinical studies to reach a definitive conclusion, taking into account characteristics of the drug product such as therapeutic window, clinical usage (acute vs. chronic administration), dosing characteristics and potential for immunogenic responses."*

Recommendation: For consistency, we suggest revising this bullet point to read as follows: *"• Although the pre- and post-change products are similar, some differences have been identified in the comparison of quality attributes and possible adverse* ***impact*** *on safety and efficacy profiles cannot be excluded. The manufacturer should consider performing nonclinical and/or clinical studies to reach a definitive conclusion, taking into account characteristics of the drug product such as therapeutic window, clinical usage (acute vs. chronic administration), dosing characteristics,* ***route of administration*** *and potential for immunogenic responses."*

Lines: 102-104: *"• Differences are so significant that it is determined that quality attributes for products are not comparable (i.e., they are not highly similar). This outcome is not within the scope of this document and is not discussed further."*

Recommendation: Significant changes resulting in non-comparable quality attributes are not included in the scope of this guideline. We suggest including text that indicates what to do in this instance.

In addition, for consistency, we suggest revising this bullet point to read as follows:
*"• Differences are so significant that it is determined that quality attributes for products are not comparable **(i.e., they are not similar)**. This outcome is not within the scope of this document and is not discussed further."*

Lines 129-132: *"• The need for stability data, including those generated from accelerated or stress conditions, to provide insight into potential product differences in the degradation pathways of the protein and, hence, potential product-related substances and product-related impurities;"*

Recommendation: For consistency, the reference to *"protein"* should be removed. Therefore the bullet point should be revised to read as follows: *"• The need for stability data, including those generated from accelerated or stress conditions, to provide insight into potential product differences in the degradation pathways and, hence, potential product-related substances and product-related impurities;"*

Lines 140-143: *"• Critical control points in the manufacturing process that affect product characteristics, e.g., the ability of downstream steps to accommodate material from a changed cell culture process, as well as the impact of the process change on the quality of downstream product;"*

Recommendation: We recommend revising this bullet point by adding some precautionary wording. We suggest revising this bullet point to read as follows: *"• Critical control points in the manufacturing process that **may** affect product characteristics, e.g., the ability of downstream steps to accommodate material from a changed cell culture process, as well as the impact of the process change on the quality of downstream product;"*

Lines 144-147: *"• Adequacy of the in-process controls including critical control points and in-process testing: In-process controls for the post-change process should be confirmed, modified, or created as appropriate, to maintain the quality of the product."*

Recommendation: We suggest revising this bullet point to read as follows:
*"• Adequacy of the in-process controls including critical control points and in-process testing: In-process controls for the post-change process should be confirmed, **adapted**, or created as appropriate, to **substantiate maintenance of** the quality of the product."*

Lines 148-151: *"• Nonclinical or clinical characteristics of the drug product: Clinical characteristics, such as therapeutic index, clinical use (e.g., acute vs. chronic*

administration), dosing, route of administration, and potential for immunogenic response of the drug product can be important in planning the comparability exercise; and"

Recommendation: For consistency of wording throughout the document, we suggest revising this bullet point to read as follows: *"• Nonclinical or clinical characteristics of the drug product: Clinical characteristics, such as therapeutic* ***window****, clinical* ***usage*** *(e.g., acute vs. chronic administration), dosing* ***characteristics****, route of administration, and potential for immunogenic response of the drug product can be important in planning the comparability exercise; and"*

Lines 152-155: *"• Each indication for a multi-indication product: The structure-activity relationships, mechanism of action, safety profile, and toxicities of the same product can vary with each clinical indication and, if so, should be addressed for each clinical indication."*

Recommendation: To remain consistent with definitions provided at the beginning of the guideline, the term *"product"* should be changed to *"drug product"*. Therefore, we suggest revising this bullet point to read as follows: *"• Each indication for a multi-indication* ***drug product****: The structure-activity relationships, mechanism of action, safety profile, and toxicities of the same* ***drug product*** *can vary with each clinical indication and, if so, should be addressed for each clinical indication."*

Lines 168-171: *"It can be difficult to ensure that the chosen set of analytical procedures for the pre-change product will be able to detect modifications of the product due to the limitations of the assays (e.g. precision, specificity, and detection limit) and the complexity of some products due to molecular heterogeneity."*

Recommendation: For clarification, we suggest revising the text to read as follows: *"It can be difficult to ensure that the chosen set of analytical procedures for the pre-change product will be able to detect modifications* ***on the post-change*** *product due to the limitations of the assays (e.g. precision, specificity, and detection limit) and the complexity of some products due to molecular heterogeneity."*

Lines 199-202: *"When process changes results in a product characterisation profile that differs from that observed in the material used during nonclinical and clinical studies or other appropriate representative materials, the significance of these alterations should be evaluated."*

Recommendation: We recommend that further guidance be provided regarding reference to *"other appropriate representative materials"*. We suggest clarifying this phrase, or deleting it.

Line 205: *"Physiochemical Properties"*

Recommendation: For editorial consistency, we suggest revising "Physiochemical Properties" to read as **"Physicochemical Properties"**.

Lines 218-221: *"The manufacturer should recognize the limitations of biological assays, such as high variability, that might prevent detection of differences that occur as a result of a manufacturing process change."*

Recommendation: For clarity, we suggest revising the text to read as follows: *"The manufacturer should **take into consideration** the limitations of biological assays, such as high variability, that might prevent detection of differences that **may** occur as a result of a manufacturing process change."*
Lines 245-246: *"The combination of analytical procedures selected should provide data to evaluate the change in purity profile in terms of the desired product."*

Recommendation: For clarity, we suggest revising the text to read as follows: *"The combination of analytical procedures selected should provide data to evaluate **if a** change in purity profile **has occurred on the post-change** product."*

Lines 247-249: *"If differences are observed in the purity and impurity profiles of the post-change product relative to the pre-change product, the differences should be evaluated to determine their impact on safety and efficacy."*

Recommendation: For clarity, we suggest revising the text to read as follows: *"If differences are observed in the purity and impurity profiles of the post-change product relative to the pre-change product, the differences should be evaluated to determine their **potential** impact on safety and efficacy."*

Lines 268-269: *"However, a widening of the acceptance criteria is generally not considered appropriate and should be justified."*

Recommendation: For clarity, we suggest revising the text to read as follows: *"However, a widening of the acceptance criteria is generally not considered appropriate **unless** justified."*

Lines 269-272: *"In some cases, additional tests and acceptance criteria on the relative abundance of specific impurities might be appropriate if the impurity profile is different following the manufacturing process changes."*

Recommendation: For clarity, we suggest revising the text to read as follows: *"In some cases, additional tests and acceptance criteria **for the control** of specific **new** impurities might be appropriate if the impurity profile is different following the manufacturing process changes."*

Lines 278-280: *"For many manufacturing process changes even slight modifications of the production procedures, including those made early in the manufacturing process for the drug substance, might cause changes in the stability of the post-change product."*

Recommendation: We recommend that text be added to clarify and provide examples of *"slight modifications"*, or to delete the sentence.

Lines 292-293: *"Accelerated and stress stability studies are often useful tools to establish degradation profiles and provide a further direct comparison of pre-changes and post-changes products."*

Recommendation: For clarity, we suggest revising the text to read as follows: *"Accelerated and stress stability studies are often useful tools to establish degradation profiles and provide a further direct comparison of pre-changes and post-changes products.* ***Stress stability studies may also be considered.***"

Lines 303-308: *"Approaches to determining the impact of any process change will wary with respect to the specific process, the product, the extent of the manufacturer's knowledge of an experience with the process, and development data generated. The manufacturer should confirm that the process controls in the modified process provide similar or more effective control of the product quality, compared to those of the original process."*

Recommendation: For clarity, we suggest revising the text to read as follows: *"Approaches to determining the impact of any process change will wary with respect to the specific process, the product, the extent of the manufacturer's knowledge* ***and his*** *experience with the process, and development data generated. The manufacturer should confirm that the process controls in the modified process provide* ***at least*** *similar control of the product quality, compared to those of the original process."*

Lines 324-325: *"To support process changes for approved products, data from commercial-scale batches are generally indicated."*

Recommendation: Some data may also come from smaller scales. For example: viral safety evaluation after a process change needs to be done in laboratory-scale. Therefore, in line with the wording used n the ICH Q5E guideline, we suggest revising this sentence to read as follows: *"To support process changes for approved products, data from batches* ***representative of the manufacturing scale of production*** *are generally indicated."*

Lines 336-338: *"When changes are made to a process, the manufacturer should demonstrate that the associated process controls, including any new ones, provide assurance that the modified process will also be capable of providing comparable product."*

Recommendation: The need for redefining process controls was previously discussed in this guideline. Therefore, we suggest revising this sentence to read as follows: *"When changes are made to a process, the manufacturer should demonstrate that the associated process controls, provide assurance that the modified process will be capable of providing* ***a*** *comparable product."*

Line 357: *"• Maintenance of the purity level"*

Recommendation: We recommend removing this bullet point since differences n the purity profile may be observed, as explained in Lines 244-256: *"Purity, Impurities, and Contaminants".*

On behalf of Aventis, we appreciate the opportunity to comment on the *ICH Q5E; Draft Guidance on Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* and are much obliged for your consideration.

Sincerely,

Steve Caffé, M.D.
Vice President, Head US Regulatory Affairs